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(71) Applicant *(for all designated States except US)*: THE UNIVERSITY OF ASTON IN BIRMINGHAM [GB/GB]; Gosta Green, Birmingham B4 7ET (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : GATE, Ernest, Nicholas [GB/GB]; 4 Aston Brook Green, Aston, Birmingham 6 (GB). SLACK, John, Alfred [GB/GB]; 10 Newlands Drive, Halesowen, West Midlands (GB). STEVENS, Malcolm, Francis, Graham [GB/GB]; 35 Chantry Road, Moseley, Birmingham 13 (GB).

(74) Agent: H.N.& W.S. SKERRETT; Rutland House, 148 Edmund Street, Birmingham B3 2LQ (GB).

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(54) Title: PHARMACEUTICAL PREPARATIONS FOR USE IN ANTITUMOUR THERAPY

(57) Abstract

An antitumour pharmaceutical preparation is made up of one or more antitumour chemotherapeutic drugs dispersed in N-methylformamide. The solvent properties of N-methylformamide are particularly useful for many antitumour drugs having low solubility or low stability in aqueous solutions and can enable these to be used in the form of more highly concentrated doses. Also the N-methylformamide can contribute to and enhance the antitumour activity without increasing bone marrow toxicity so that the coadministration thereof leads to beneficial combination chemotherapy.

P5-benoxiden

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PHARMACEUTICAL PREPARATIONS FOR USE IN ANTITUMOUR THERAPY

The present invention relates to pharmaceutical preparations for use in antitumour therapy.

Of the many known chemotherapeutic agents which are active against various malignant tumours in humans and other mammals, and which constitute the presently recognised range of antitumour drugs, many are unstable solids having low solubility in solvents suitable for making up solutions appropriate for parenteral administration, and the great majority exhibit significant bone marrow toxicity, i.e. have myelosuppression characteristics.

The low solubility of many of the known antitumour drugs in water or other common administrable solvents, as mentioned above, is important in limiting dosage amounts and/or in restricting the form in which the drugs can be prepared and administered, thereby restricting the method of use and the manner of optimising the clinical therapy treatment with such drugs.

Moreover, the bone marrow toxicity referred to is a major factor in practice in limiting the maximum dosage and treatment schedule that can safely be employed and tolerated in antitumour chemotherapeutic clinical use. Frequently, for example, a difficult choice must be made between administering a large dose at infrequent intervals, sufficient to allow time for bone marrow activity to be restored, and administering at more frequent intervals much smaller doses which are each less toxic but which are also each less effective against the tumour growth.

The present invention seeks to provide a pharmaceutical preparation which enables the above difficulties to be overcome or reduced and which gives more scope for clinical treatment to be optimised or carried out with enhanced antitumour effects.

According to the invention, a pharmaceutical preparation for use in antitumour therapy is composed of at least one antitumour chemotherapeutic drug dispersed in N-methylformamide solvent carrier or substrate medium.

The term "antitumour chemotherapeutic drug" as used herein signifies any chemical compound, other than N-methylformamide itself, which has a recognisable activity against at least certain cancers or malignant tumours.

In many cases, in using the pharmaceutical preparations in accordance with the invention, the N-methylformamide will also provide an advantageous further and additional therapeutically active antitumour constituent as well as acting as a solvent carrier or substrate medium for the other drug or drugs.

As hereinafter explained, in general the invention will be of particular benefit where the antitumour chemotherapeutic drug or drugs constituent has a clinically restrictive low solubility at least in aqueous solutions and/or elicits clinically restrictive bone marrow toxicity or myelosuppression effects in therapeutic use.

It has been found that N-methylformamide generally exhibits excellent solvent properties and useful stabilising characteristics for the known solid antitumour drugs, even those whose low solubility and/or instability in aqueous solution has hitherto given problems in using them, or in restricting their manner of use, at desired dosage levels, or which has prevented the making up of concentrates in liquid or suspension form for storage and transport. With the N-methylformamide providing a solvent vehicle or substrate medium, however, in which the other antitumour drug or drugs is or are dispersed by being completely dissolved or suspended (for instance as a colloidal suspension) therein, the preparations in accordance with the invention can be readily made up into liquid doses suitable for administering by various methods without any serious sterilisation or other hygenic problems. Doses of the preparations may, for example,

be contained or provided in ampoules for injection (in this case the doses may, or may not, require further dilution before administration with a suitable solution, e.g. water for injections BP, sodium chloride saline injection BP or 5% dextrose injection BP), in suppositories, in measured volumes for mixing for oral administration, or even possibly in aerosols for inhalation, in addition of course to being mixed with other conventional diluents or binders for making up into parenteral dosage forms, syrups, creams and ointments (e.g. for transdermal delivery of the drug or drugs), capsules, tablets etc. Also, the preparations can be manufactured, distributed and stored as liquid concentrates suitable for diluting to prepare the doses for clinical administration.

The fact that solid antitumour drugs of low solubility in water or other conventional administrable solvents can now be provided in liquid doses of relatively high concentration by exploiting the solvent properties of N-methylformamide also gives rise to the possibilities of being able to change the route of administration leading to increased tolerance levels and/or improved bioavailability and effectiveness. For example, those drugs at present given orally may in some cases be more effective clinically if now given by parenteral administration, and vice versa, using such drugs in the form of a preparation in accordance with the present invention.

Also, and most importantly, by incorporating N-methylformamide in the preparation, the N-methylformamide can itself contribute and add to the antitumour activity for at least certain types of tumours as already indicated, and this effect appears to be exhibited without introducing any significant bone marrow toxicity or additional increase in the level of bone marrow toxicity or myelosuppression effects arising from the other said antitumour drug constituent or constituents.

There can, therefore, also be a co-operative relationship enabling doses of pharmaceutical preparations in accordance with the invention to be made up for clinical use in which the maximum

clinically tolerable amount of an antitumour myelosuppressive drug constituent or constituents can be combined with the N-methylformamide to act simultaneously therewith such as to provide, at least over an administrative period of therapy, an antitumour effect significantally greater than could be provided by the former used alone at a maximum clinically acceptable dosage level. The phrase "administrative period of therapy" is used in this context to denote a period embracing a complete course of treatment, including at least two successive dose administrations, as determined by the clinician.

Also, with such preparations in accordance with the invention, a greater antitumour activity may be obtained in some cases than would be expected from the amounts or quantities of the individual constituents used acting separately.

Although antitumour activity of N-methylformamide has previously been the subject of some previous studies and interest, an apparent hepatotoxic effect reported in 1956 (Myers et al, Cancer, 9, 949) has discouraged extended clinical trials. However, it has now been found that the reported hepatotoxic effect does not appear to be as serious as was originally thought since it is generally reversible and can be controlled by a proper treatment routine, and in any event it is believed that the combinative or co-operative relationship of N-methylformamide in co-administration with known myelosuppressive antitumour drugs represents a concept which has not been previously investigated and which unexpectedly shows a high degree of promise for more effective chemotherapeutic treatment of tumours.

As indicated, the invention may be applied generally to a wide range of antitumour drugs effective to a greater or lesser extent in treating a variety of tumours. Such drugs may include the compounds known as Hexamethylmelamine, Busulphan, Carmustine (BCNU), Chlorambucil, Cyclophosphamide, Estramustine Phosphate, Ethoglucid, Ifosfamide, Lomustine (CCNU), Melphalan, Mitobronitol, Mustine Hydrochloride, Thiotepa, Treosulphan, Uramustine, Actinomycin D, Bleomycin Sulphate, Daunorubicin Hydrochloride, Doxorubicin

Hydrochloride, Mithramycin, Mitomycin, Cytarbine, Fluorouracil, Mercaptopurine, Methotrexate, Thioguanine, Vinblastine Sulphate, Vincristine Sulphate, Vindesine Sulphate, Cisplatin (CDDP), Colaspase(Asparaginase), Dacarbazine (DTIC), Hydroxyurea, Procarbazine Hydrochloride, Razoxane, Tamoxifen Citrate, Teniposide, Etoposide, Amsacrine, Mitoxanthrone and other compounds listed, for example in the publication entitled "Chemical structures of interest to the Division of Cancer Treatment", Volume 3 (1983) by N. R. Lomax and V. L. Narayanan of the Drug Synthesis and Chemistry Branch, Development Therapeutics Program, National Cancer Institute, of Bethesda, Maryland, U.S.A., as being drugs having antitumour activity. In particular, the invention is especially useful in connection with drugs of the alkylating agent class such as cyclophosphamide, and the nitrosoureas, or hexamethylmelamine and other antitumour drugs having a low solubility in aqueous solutions and/or having high bone marrow toxicity or myelosuppressive properties. For a discussion of bone marrow toxicity or myelosuppressive properties relevant to many of the above-mentioned drugs, reference may be made to a paper entitled "Hematologic Complications of Cancer Chemotherapy" by H. Clark Hoagland published in Seminars in Oncology, Vol. 9, No. 1 (March), 1982.

With regard to the solubility and stability aspect of antitumour drugs dispersed in N-methylformamide acting as a solvent carrier, hexamethylmelamine may be quoted as one example. This has a reported solubility of 0.091mg/ml in M/200 phosphate buffer at a pH of 7 at 25°C giving a maximum concentration in solution of 0.0091% w/v. In contrast, it has been found that this drug has a solubility in N-methylformamide of 5mg/ml (at 20°C) giving stable solutions with a concentration of 0.5% w/v, that is, the solubility in N-methylformamide is approximately fifty times greater than in water.

In another example, reference may be made to methotrexate. Methotrexate is a clinically active drug which acts as an anti-metabolite by inhibition of dihydrofolate reductase. It is commonly administered by a variety of routes but for high doses the favoured

route is by intravenous infusion. The drug is used in the treatment of acute lymphocytic leukaemia, choriocarcinoma and cancers of the head, neck and lung. In one experiment methotrexate was dissolved (as the free acid) in 100% N-methylformamide and was seen to have a very satisfactory solubility of 172 mg/ml and this solution had a $t_{90\%}$ of 45 days ($t_{90\%}$ denotes the time taken for 10% of the drug to degrade at room temperature).

In another example reference may be made to cyclophosphamide. Cyclophosphamide is a commonly used antitumour drug which requires prior metabolism, in the liver, to release its active form. It is used to treat solid tumours and a wide range of haematological malignancies. The solubility of cyclophosphamide in various strengths of N-methylformamide and the stability of these solutions (at room temperature) are summarised below:

Solubility (mg/ml)	% N-methylformamide	t_{90} (Days)
	(in McIlvaine's buffer pH 7.4)	
17	0	8
194	30	11
920	100	58

It can be seen that both the solubility and stability of cyclophosphamide are markedly enhanced by N-methylformamide.

In a further example, reference may be made to doxorubicin. Doxorubicin is one of the most successful antitumour drugs. It is used in the treatment of solid tumours and also acute leukaemias. It is normally administered via a fast-running intravenous infusion due to the problems of severe local pain due to tissue extravasation. The solubility of doxorubicin in buffer at pH 4.0 is 89 mg/ml whereas in buffer and 30% N-methylformamide this solubility is increased to 116 mg/ml. The stabilities of these solutions at room temperature are as

follows:

$t_{90\%}$ (Days)	% N-methylformamide (in buffer pH 4.5)
25	0
38	30

It can be seen that the stability of doxorubicin in aqueous solutions is enhanced by N-methylformamide.

By way of example of the results of some of a series of preliminary experimental laboratory work on animals, in connection with the antitumour properties of N-methylformamide and its suitability for use in conjunction with other antitumour drugs, reference may be made to the accompanying diagrams.

The two diagrams, labelled Figures 1 and 2, relate to tests on the effect of cyclophosphamide and N-methylformamide, used separately and together, on mice (strain BDF_1) implanted with 10^6 M5076 sarcoma cells. Figure 1 shows the mean tumour volumes of the M5 sarcoma bearing mice treated with these drugs when, on day 12 after tumour implantation, several therapy routines were initiated as set forth in the key tables appended to the diagram. Figure 2 shows the variation in white blood cell counts (an indication of bone marrow toxicity) for each of the routines listed and for control animals. The results of these and other experiments showed:

1. High-dose cyclophosphamide treatment results, as already known, in severe leukopenia in BDF_1 mice.

2. N-methylformamide treatment, initiated 3 days after treatment with high-dose cyclophosphamide, produced no increased leukopenia over and above that of the cyclophosphamide treatment alone, and did not inhibit recovery of the bone marrow from the cyclophosphamide induced leukopenia, but an

improved antitumour effect against the M5076 sarcoma was observed.

3. A repeat injection of cyclophosphamide, 3 days after the first, results in an extended leukopenia and yet does not produce as potent an antitumour effect as the addition of N-methylormamide to the initial injection of cyclophosphamide.

4. Whereas treatment with cyclophosphamide at 320 mg/kg resulted in 1 out of 10 deaths of the animals, treatment with cyclophosphamide at 320 mg/kg plus N-methylformamide at 200 mg/kg/day for 10 days produced no deaths, indicating the combination to be no more toxic than cyclophosphamide alone.

5. In addition, the combination of drugs was not significantly hepatotoxic at the dose levels used.

As mentioned, the above were merely preliminary laboratory experiments and the cyclophosphamide and the N-methylformamide, even when both used for treatment, were in fact administered separately for obtaining the data required. As already indicated, however, it is a feature of the invention in practice for clinical use that the N-methylformamide and the other drug or drugs are in fact utilised together and administered simultaneously as components or constituents of the formulation providing a single pharmaceutical preparation which exploits the solvent properties of N-methylformamide and/or which is particularly effective for combination chemotherapy.

In other similar experiments for testing the effect on tumour growth, using hexamethylmelamine instead of cyclophosphamide, with and without N-methylformamide, and using also N-methylformamide on its own, an enhanced antitumour effect of the hexamethylmelamine and N-methylformamide in combination has again been observed without any increased toxicity. And again, by way of example, experiments involving the co-administration of N-methylformamide and the drug known as Cisplatin (CDP) which has nephrotoxic characteristic have

indicated enhanced antitumour activity in relation to M5076 sarcoma in BDF_1 mice without causing any increased nephrotoxic damage and myelosuppression or any serious increase in hepatotoxicity.

To illustrate further the practical application of the invention, reference may be made to the following examples of formulations which may be suitable for antitumour thereapeutic use at least in certain cases:

Example 1

Etoposide (100 mg) is dissolved in a mixture of N-methylformamide (1.5g) anhydrous citric acid (10 mg), benzyl alcohol (150 mg), purified polysorbate 80 (400 mg), polyethylene glycol 300 (3.25g) and ethyl alcohol (0.2g). The solution may be sterilised by filtration or autoclaving and may be diluted with Sodium Chloride Injection BP or Dextrose Injection BP before administration by slow intravenous infusion.

N.b. The doses of this etoposide and N-methylformamide preparation administered in the clinic may be modified according to the clinical status of the patient. Accordingly, considerable variation in the quantities of these agents, and therefore of the quantities of the citric acid, benzyl alcohol, purified polysorbate 80, polyethylene glycol 300 and ethyl alcohol required to effect the preparation of a suitable dosage form may be permitted.

Example 2

Amsacrine (75 mg) is dissolved in N-methylformamide (1.5g). The solution may be sterilised by filtration, or, alternatively, a sterile freeze-dried sample of amsacrine may be admixed, aseptically, with sterile N-methylformamide.

Before administration the solution, prepared as above, may be added, aseptically, to 13.5 ml. of 0.0353M L-lactic acid to give a combined solution suitable for parenteral administration. This combined solution is physically incompatible with Sodium Chloride Injection B.P.

Example 3

A sample of sterile lyophilised 6-mercaptopurine sodium salt (0.5g) and sterile N-methylformamide (1.5 ml) are combined aseptically. This mixture is intended to be reconstituted with sterile water for Injections BP to produce a solution containing, in each 1 ml, 10 mg of mercaptopurine sodium salt.

Before administration the solution should be diluted further with Sodium Chloride Injection BP or Dextrose Injection BP to provide a final concentration of 1-2 mg/ml of mercaptopurine sodium salt.

CLAIMS

1. A pharmaceutical preparation for use in antitumour therapy characterised in that it is composed of at least one antitumour chemotherapeutic drug dispersed in an N-methylformamide solvent carrier or substrate medium.

2. A pharmaceutical preparation as claimed in Claim 1, wherein the concentration of the antitumour chemotherapeutic drug or drugs in the N-methylformamide solvent carrier or substrate medium is greater than the maximum possible concentration thereof in aqueous solution under the same environmental conditions.

3. A pharmaceutical preparation as claimed in Claim 1 or 2, wherein the antitumour chemotherapeutic drug or drugs constituent elicits clinically restrictive bone marrow toxicity or myelosuppression effects in therapeutic use.

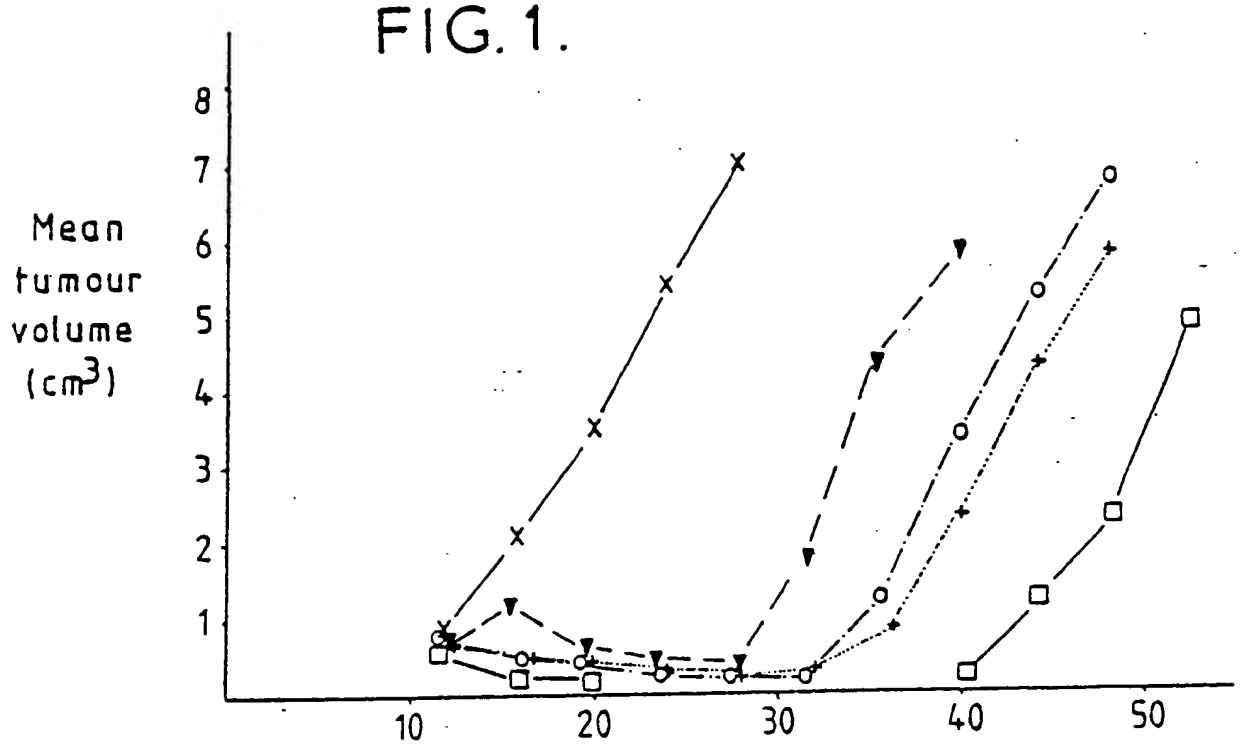
4. A pharmaceutical preparation as claimed in any of the preceding claims wherein the solvent carrier or substrate medium consists of undiluted N-methylformamide.

5. A pharmaceutical preparation as claimed in any of the preceding claims where the or at least one said antitumour chemotherapeutic drug is selected from the group of compounds comprising: Hexamethylmelamine, Busulphan, Carmustine(BCNU), Chlorambucil, Cyclophosphamide, Estramustine Phosphate, Ethoglucid, Ifosfamide, Lomustine (CCNU), Melphalan, Mitobronitol, Mustine Hydrochloride, Thiotepa, Treosulphan, Uramustine, Actinomycin D., Bleomycin Sulphate, Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Mithramycin, Mitomycin, Cytarbine, Fluorouracil, Mercaptopurine, Methotrexate, Thioguanine, Viniblastine Sulphate, Vincristine Sulphate, Vindesine Sulphate, Cisplatin (CDDP), Colaspase (Asparaginase), Dacarbazine (DTIC), Hydroxyurea, Procarbazine Hydrochloride, Razoxane, Tamoxifen Citrate, Teniposide, Etoposide, Amsacrine, Mitoxanthrone.

6. A pharmaceutical preparation as claimed in any of Claims 1 to 4 where the or at least one said antitumour chemotherapeutic drug is selected from the group of compounds listed as being drugs having antitumour activity in the publication entitled "Chemical structure of interest to the Division of Cancer Treatment", Volume 3 (1983) by N. R. Lomax and V. L. Narayanan of the Drug Synthesis and Chemistry Branch, Development Therapeutics Program, National Cancer Institute of Bethesda, Maryland, U.S.A.

7. A pharmaceutical therapeutic composition comprising a preparation as claimed in any of the preceding claims made up in dosage form in combination with a pharmaceutically acceptable diluent or binder.

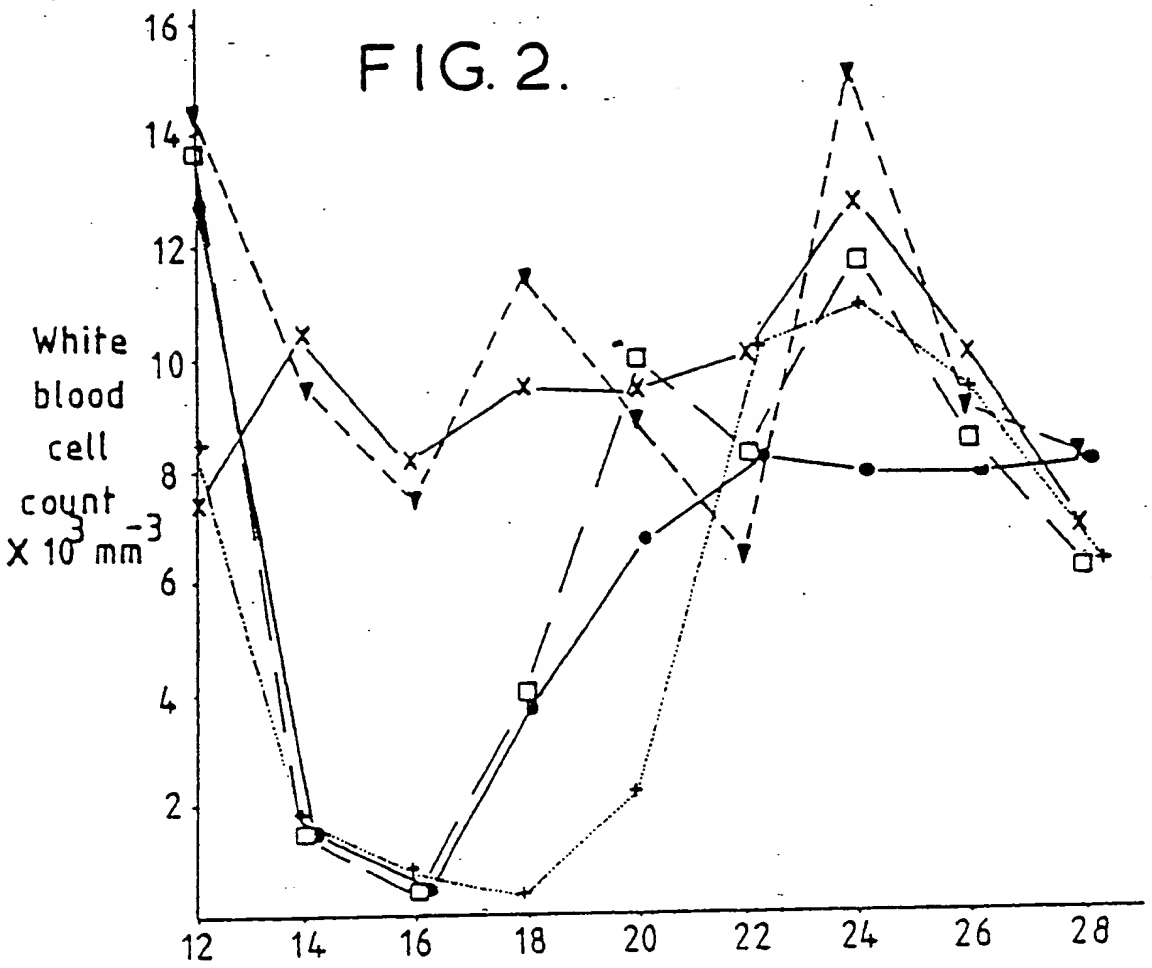
FIG. 1.



	Treatment	Dose *	Schedule
o—o	Cyclophosphamide	320	Day 12
+—+	Cyclophosphamide	160	Days 12 and 15
▼—▼	N-Methylformamide	200	Days 15 — 24
□—□	Cyclophosphamide	320	Day 12
	N-Methylformamide	200	Days 15 — 24
x—x	Control	—	

* mg / kg/day

FIG. 2.



	Treatment	Dose *	Schedule
□— —□	Cyclophosphamide	320	Day 12
+·····+	Cyclophosphamide	160	Days 12 and 15
▼- - - -▼	N-Methylformamide	200	Days 15 — 24
●——●	Cyclophosphamide	320	Day 12
	N-Methylformamide	200	Days 15 — 24
x——x	Control	—	

* mg/kg/day

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 83/00257

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: A 61 K 47/00; A 61 K 45/06; A 61 K 9/10; A 61 K 31/70; A 61 K 31/52; A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	Chemical Abstracts, volume 97, no. 11, 13 September 1982, Columbus, Ohio (US) A. Gescher et al.: "N-Methylformamide: antitumor activity and metabolism in mice", see page 20, abstract 84663g, Br.J. Cancer 1982, 45(6) 843-50 (Eng.) --	1-7
A	Chemical Abstracts, volume 77, no. 13, 25 September 1972, Columbus, Ohio (US) A. Furst et al.: "Experimental chemo-therapy of nickel-induced fibrosarcomas" see page 89, abstract 84221y, Oncology 1972, 26(4), 422-6 (Eng.) --	1-7
A	Chemical Abstracts, volume 49, no. 22, 25 November 1955, Columbus, Ohio (US) A. Furst et al.: "Retardation of growth of Ehrlich ascites tumor by formamides and related compounds", see column 16225ef, Cancer Research 15, 294-9 (1955) --	1-7

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [5]	Date of Mailing of this International Search Report [5]
19th January 1984	17 FEV. 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, volume 54, no. 13, 10 July 1960, Columbus, Ohio (US) M.N. Teller et al.: "Transplantable human tumors in experimental chemotherapy. A comparison with animal tumor systems"see column 13439d, Cancer Research 20, 112-19 (1960)	1-7
P,A	Chemical Abstracts, volume 99, no. 7, 15 August 1983, Columbus, Ohio (US) W.R. Cobb et al.: "Activity of two phase I drugs N-methylformamide (NSC-3051) and Echinomycin (NSC-526417) against fresh surgical explants of human tumors in the 6-day subrenal capsule (SRC) assay", see page 26, abstract 47637x, Invest. New Drugs 1983, 1(1), 5-9	1-7
A	EP, A, 0042553 (BRISTOL-MYERS COMPANY) 30 December 1981	1-7

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 83/00257 (SA 5909)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/02/84

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0042553	30/12/81	JP-A-	57028006	15/02/82
		AU-A-	7083781	17/12/81

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